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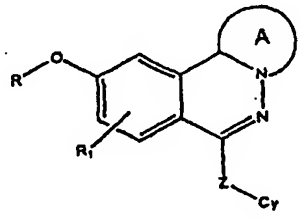
(54) Title: TRICYCLIC PHTHALAZINE DERIVATIVES AS PHOSPHODIESTERASE 4 INHIBITORS

(57) Abstract

Tricyclic phthalazine compounds of formula (I) wherein A is a 5–7 membered heterocycle containing from 1 to 4 nitrogen atoms, optionally partially or totally unsaturated, and optionally substituted by a (C_{1-4})alkyl group in turn optionally substituted; Z is NH, methylene, a C_{2-6} alkylene chain optionally branched and/or unsaturated and/or interrupted by a C_{5-7} cycloalkyl residue; Cy is phenyl or heterocycle optionally substituted by one or more substituents, or a COR_4 group wherein R_4 is hydroxy, alkoxy, amino optionally substituted by one or two (C_{1-6})alkyl groups or by hydroxy; R is a (C_{1-6})alkyl or polyfluoro(C_{1-6})alkyl group; R_1 is hydrogen; a (C_{1-8})–alkyl, (C_{2-8})–alkenyl or (C_{2-8})–alkynyl group optionally substituted by hydroxy, oxo, aryl or heterocycle, and optionally interrupted by one or more heteroatoms or heterogroups; a (C_{1-4})alkoxy group or a (C_{4-7})cycloalkoxy group optionally containing an oxygen atom and optionally substituted by a polar substituent in the cyclic moiety, aryloxy, aryl–(C_{1-10})–alkoxy; the N–O derivatives and the pharmaceutically acceptable salts thereof are described. The compounds of formula (I) are PDE 4 inhibitors.



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TRICYCLIC PHTHALAZINE DERIVATIVES AS PHOSPHODIESTERASE 4 INHIBITORS

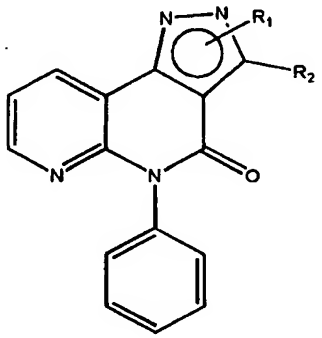
The present invention relates to tricyclic derivatives, to the pharmaceutical compositions containing them and to their use as phosphodiesterase 4 inhibitors.

Phosphodiesterases are a family of isoenzymes which constitute the basis of the main mechanism of cAMP (cyclic adenosine-3',5'-monophosphate) hydrolytic inactivation. cAMP has been shown to be the second messenger mediating the biologic response to many of hormones, neurotransmitters and drugs [Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, 17-29, 1973]. When the suitable agonist binds to the cell surface, the adenylated cyclase activates and turns Mg^{2+}-ATP into cAMP. cAMP modulates the activity of the majority, if not of all the cells contributing to the pathophysiology of various respiratory diseases, both of allergic origin and not. It follows that an increase of the cAMP concentration yields beneficial effects such as airway smooth muscle relaxation, inhibition of the mast cell mediator release (basophil granulose cells), suppression of the neutrophil and basophil degranulation, inhibition of the monocyte and macrophage activation. Thus, compounds able of activating adenylate cyclase or of inhibiting phosphodiesterases could suppress the undesired activation of the airway smooth muscle and of a great number of inflammatory cells.

In the phosphodiesterase family there is a distinct group of isoenzymes, phosphodiesterases 4 (hereinafter PDE 4) specific for the cAMP hydrolysis in the airway smooth muscle and inflammatory cells (Torphy, "Phosphodiesterase Isoenzymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma. Barnes, ed. IBC Technical Services Ltd, 1989). Studies carried out on this enzyme show that its inhibition yields not only the airway smooth muscle relaxation, but also the suppression of mastocyte, basophil and neutrophil degranulation, so as the inhibition of the monocyte and neutrophil activation. In addition, the action of PDE 4 inhibitors is markedly strengthened when the adenylate cyclase activity of the target cells is increased by endogenous hormones, as it happens *in vivo*. Thus PDE 4 inhibitors are effective in the therapy of asthma. Such compounds offer a unique approach to the therapy of various respiratory diseases, both of allergic origin and not, and possess significant therapeutic advantages over the current therapy.

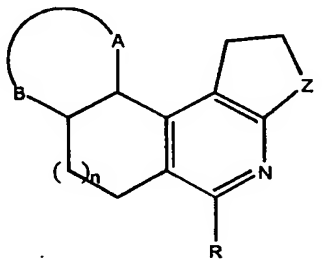
The excessive or irregular production of tumour necrosis factor (hereinafter TNF_α), a cytokine with pro-inflammatory activity produced by various kinds of cells, affects the mediation or the exacerbation of many pathologies such as, for example, the adult respiratory distress syndrome (ARDS) and the chronic pulmonary inflammatory disease. Therefore compounds able to control the negative effects of TNF_α, i.e. the inhibitors of this cytokine, are to be considered as useful against many pathologies.

The patent EP 0 526 840 (iKyowa Hakko Kogyo) claims compounds of formula



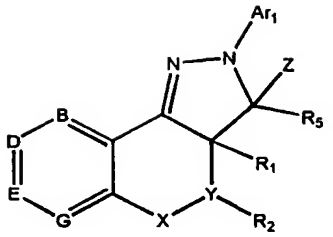
wherein R_1 is hydrogen, (C_{1-6})alkyl, (C_{7-15})arylalkyl or optionally substituted aryl; and R_2 is hydrogen, (C_{1-6})alkyl, thienyl or optionally substituted aryl. These compounds are said to be active, *inter alia*, as antiinflammatories, immunosuppressives, bronchodilators.

The patent application JP 09227563 (Lederle Japan) describes compounds of formula



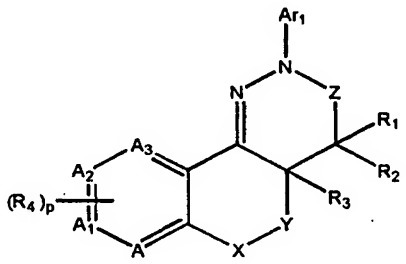
wherein R is an optionally substituted amino group, Z is S or O, A and B form a benzene ring or are absent, and n is 0-2. These compounds are useful as bronchodilators, antiasthmatics, antihypertensives and anticholesterolemics.

The patent application WO 97/34893 (Astra) describes compounds of formula



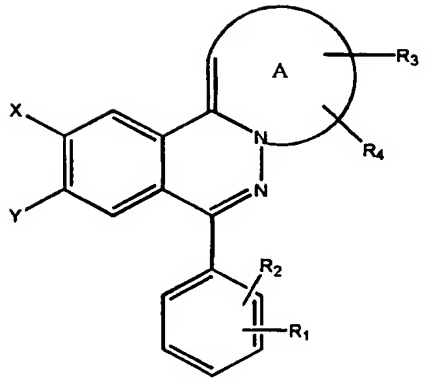
wherein B, D, E and G may form a benzene ring optionally substituted by alkoxy; X is C=O, C=S, C=NR, CR_3R_6 or NR_4; R_3 is H or forms a bond with R_2; R_4 is lower alkyl or forms a bond with R_2; R_6 may be H, lower alkyl optionally substituted by phenyl, or cycloalkyl, phenyl, etc.; Y is N or CR; R_2 may be H, lower alkyl optionally substituted by phenyl, COOR, NR'R", OR, F, or cycloalkyl or may form a bond with one of R_1, R_3 and R_4; R_1 may be OH or lower alkyl or may form a bond with one of R_2 and R_5; R_5 is a bond with R_1 or R_8; Z is OR_8 or O; and Ar_1 may be optionally substituted phenyl, pyridyl, pyrimidyl. These compounds have an antiinflammatory activity.

The patent application WO 98/09969 (Astra) describes compounds of formula



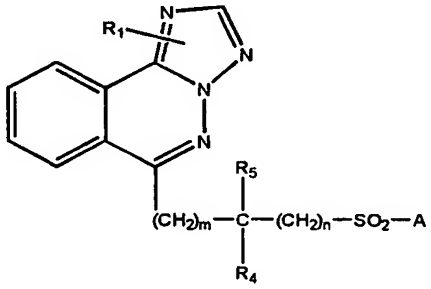
wherein A, A_1, A_2 and A_3 may be CH or CR_4; X may be CH_2 or O; Y may be a bond, CH_2, C=O, C substituted by alkyl in turn substituted by a cyclic residue; Z is a bond or CH_2; R_1 is hydrogen, lower alkyl or alkoxy; R_2 and R_3 are hydrogen or form a bond; and R_4 may be optionally substituted alkoxy. These compounds have an antiinflammatory and antiallergic activity.

The patent application DE 19617862 (Schering AG) describes compounds of formula



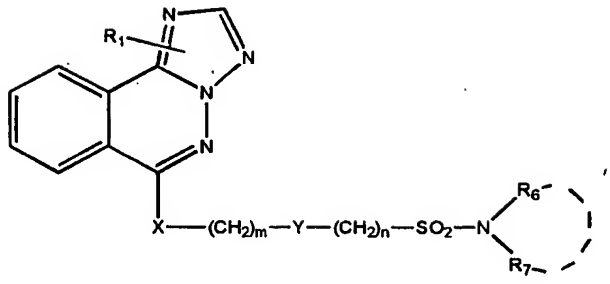
wherein, *inter alia*, R_1 and R_2 are H, alkyl, nitro, halogen, amino, lower alkoxy, CF_3; R_3 and R_4 are H, alkyl, aryl, heteroaryl or cycloalkyl; X=H; Y is alkoxy or X+Y= $-O-(CH_2)_n-O-$; n=1-3; and A is a 5-member heterocycle having from 1-3 nitrogen atoms. These compounds are inhibitors of glutamate receptor.

The patent application EP 0 548 923 (Takeda Chemical Ind.) describes, *inter alia*, compounds of formula

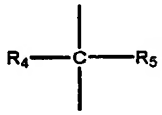


wherein R_1 is H or a lower alkyl group or a halogen atom; R_4 and R_5 are H or a lower alkyl group or form a 3-7 membered cycle optionally containing a heteroatom together with the carbon atom to which they are bound; A is an optionally substituted amino group; and m, n =1-4. These compounds are antiallergics, antiinflammatories and anti-PAF (anti-piastrinic activating factor), and are useful as antiasthmatics. In fact, these compounds act through an anti-PAF mechanism which makes them bronchodilators.

Similar compounds are claimed in the patent application EP 0 620 224 (Takeda Chemical Ind.) which illustrates, *inter alia*, the general formula

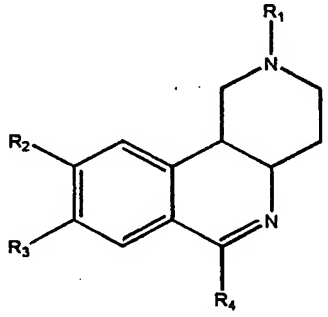


wherein R_1 is H or a lower alkyl group or a halogen atom; X is an oxygen or sulphur atom or a $-CH_2-$ group; Y is a group



wherein R_4 and R_5 are H or a lower alkyl group, or is a 3-7 membered cycle optionally containing a heteroatom; R_6 and R_7 are H, an optionally substituted lower alkyl, cycloalkyl or aryl or together with the nitrogen atom to which they are bound form a heterocycle; and m, n=0-4. These compounds have the same activity claimed in the just above cited patent application.

The patent application WO 98/21208 (Byk Gulden Lomberg) claims PDE3 and PDE4 inhibitors of formula

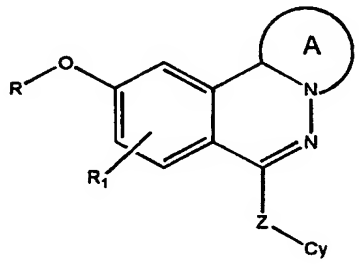


wherein, *inter alia*, R_1 is an alkyl group; R_2 and R_3 are hydroxy, optionally fluorinated alkoxy, cycloalkoxy and cycloalkylmethoxy; and R_4 is a phenyl group substituted by carboxy, amido or alkoxycarbonyl and optionally substituted by halogen, alkyl, CF_3, nitro or hydroxy. These compounds are said to be useful in the treatment of pathologies of the airways and/or of dermatosis.

It has now surprisingly been found a new class of phthalazine derivatives able to inhibit PDE

4 and TNF_{α}.

Therefore the present invention relates to compounds of formula



(I)

wherein

A is a 5-7 membered heterocycle containing from 1 to 4 nitrogen atoms, optionally partially or totally unsaturated, and optionally substituted by a (C_{1-4})alkyl group in turn optionally substituted;

Z is NH, methylene, a C_{2-6} alkylene chain optionally branched and/or unsaturated and/or interrupted by a C_{5-7} cycloalkyl residue;

Cy is phenyl or heterocycle optionally substituted by one or more substituents, or a COR_4 group wherein R_4 is hydroxy, alkoxy, amino optionally substituted by one or two (C_{1-6})alkyl groups or by hydroxy;

R is a (C_{1-6})alkyl or polyfluoro(C_{1-6})alkyl group;

R_1 is hydrogen; a (C_{1-8})-alkyl, (C_{2-8})-alkenyl or (C_{2-8})-alkynyl group optionally substituted by hydroxy, oxo, aryl or heterocycle, and optionally interrupted by one or more heteroatoms or heterogroups; a (C_{1-4})alkoxy group or a (C_{4-7})cycloalkoxy group optionally containing an oxygen atom and optionally substituted by a polar substituent in the cyclic moiety, aryloxy, aryl-(C_{1-10})-alkoxy;

the N→O derivatives of the compounds of formula I and the pharmaceutically acceptable salts thereof.

Preferred compounds according to the invention are those of formula I wherein Z is methylene or a C_{2-6} alkylene chain.

Still more preferred compounds according to the invention are those of formula I wherein Z is methylene or a C_{2-6} alkylene chain; and Cy is a heterocycle optionally substituted by one or more substituents.

Still more preferred compounds according to the invention are those of formula I wherein Z is methylene; and Cy is pyridine substituted by two substituents.

The compounds of formula I can have one or more asymmetric centres and therefore they can be in the form of stereoisomers. Object of the present invention are compounds of formula I in the form of diastereoisomeric mixtures as well as of single stereoisomers.

The compounds of formula I are active as PDE 4 and TNF_α inhibitors and thus are used as therapeutic agents in allergic and inflammatory pathologies such as, for example, emphysema, chronic bronchitis, asthma and allergic rhinitis.

For substituent Cy, as heterocycle it is particularly meant pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, piperazine, triazine, morpholine, pyrrolidine, pyrroline, imidazoline, pyrazoline, pyrazolidine, imidazolidine, piperidine, furan, pyran, isothiazole, isoxazole, thiophene and the like.

The optionally present substituents can be oxo, nitro, carboxy, halogen, that means a flúorine, chlorine, bromine or iodine atom. As "polar substituent" they are meant those groups made by atoms having a different electronegativity, so forming a dipole, such as, for example, a hydroxy or keto group.

Specific examples of alkyl groups are methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, 1-methyl-butyl, 2-ethyl-propyl, 3-methyl-butyl, 3-methyl-2-butyl, n-hexyl, heptyl, octyl and the like; examples of substituents optionally present on the alkyl groups are (C_{1-6})alkoxy groups and amino groups mono- or di-substituted by (C_{1-4})alkyl groups.

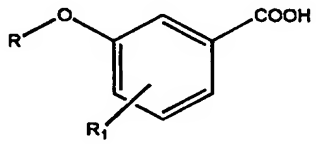
As (C_{4-7})cycloalkyl group cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl are meant, while the aryl and the aryl moiety of the aryl-(C_{1-10})alkyl substituent mean an aromatic ring of 6-10 carbon atoms such as, for example, phenyl, naphthyl, indanyl, and the like, and, consequently, as aryl-(C_{1-10})-alkyl substituent, benzyl, phenylethyl, phenyl-pentyl, indanyl-pentyl and the like.

The oxidised form N→O, when present, can be on the nitrogen atoms of the phthalazine ring as well as on those on Cy.

Pharmaceutically acceptable salts of the compounds of formula I are those with organic and inorganic acids, such as, for example, hydrochloric, hydrobromic, hydroiodic, sulfuric,

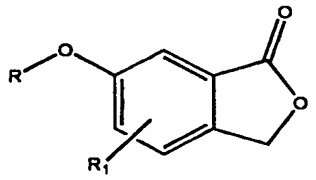
phosphoric, nitric, acetic, benzoic, maleic, fumaric, succinic, tartaric, citric, aspartic, methanesulfonic and 3,7-di-t.butylnaphthalen-1,5-disulfonic (dibudinic acid), or with inorganic bases such as, for example, sodium or potassium hydroxide, sodium bicarbonate.

The synthesis of the compounds of formula I proceeds according to methods known to the skilled in the art. For example, when a compound of formula I wherein Z is different from NH is desired, the synthesis can start from an acid of formula



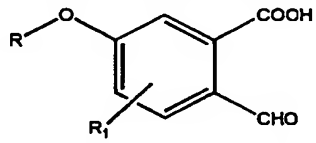
(II)

wherein R and R_1 are as above defined, which by reaction with formaldehyde/HCl gives a compound of formula



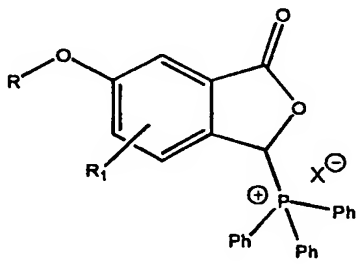
(III)

wherein R and R_1 are as above defined. This is oxidised, for example, with benzoyl peroxide/N-bromo-succinimide, and then hydrolysed to give a compound of formula



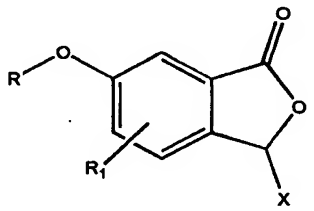
(IV)

wherein R and R_1 are as above defined, which is treated with a hydrohalogenidric acid (HX) and triphenylphosphine to give a compound of formula



(V)

wherein R and R_1 are as above defined. This compound can be also obtained from compound III by radicalic halogenation with, for example, azaisobutyronitrile or benzoyl peroxide/N-bromo- or chloro-succinimide to give the compound of formula



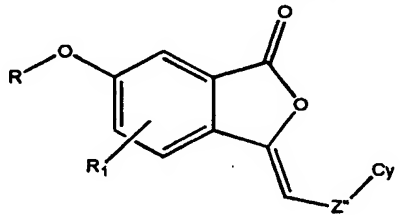
(IIIa)

wherein R and R_1 are as above defined, and X is chlorine or bromine, which gives compound V by treatment with triphenylphosphine.

Compound V is treated with an aldheyde of formula

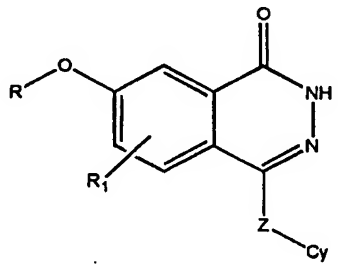
Cy-Z"-CHO (VI)

wherein Cy is as above defined and Z" is a C_{1-5} alkylene chain optionally branched and/or unsaturated and/or interrupted by a C_{5-7} cycloalkyl residue, or it is absent, in the presence of an organic base such as, for example, triethylamine, and gives a compound of formula



(VII)

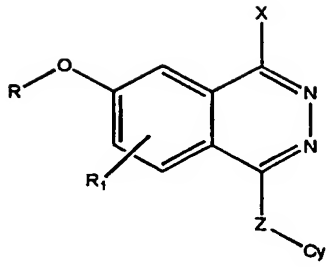
wherein R, R_1, Z" and Cy are as above defined. This is reacted with hydrazine to give a compound of formula



(VIII)

wherein R, R_1, and Cy are as above defined and Z has the meanings reported in formula I but amino, which is treated with a halogenating agent, such as phosphoryl chloride or bromide,

to give a compound of formula



(IX)

wherein R, R_1 and Cy are as above defined, X is chlorine or bromine, and Z is different from amino, which istreated with a suitable nucleophile such as, for example, sodium azide or sodium tetrazolate, or with hydrazine and then with a suitable acylating agent such as, for example, acetic anhydride or acetyl chloride. and gives the desired compound of formula I.

The synthesis of the N-oxides of the compounds of formula I occurs by treating the compounds of formula I with peracids such as. for example, m-chloroperbenzoic acid.

The preparation of the salts of the compounds of formula I is carried out according to conventional methods.

The compounds of formula I are PDE 4 inhibitors as showed by the *in vitro* enzymatic inhibition tests (example 18), and furthermore are able to inhibit the TNF_α release.

It is apparent how these enzymatic selectivity and specificity features combined with the lack of activity on the cardiovascular system make the compounds of formula I specifically suitable for treating pathologies involving PDE 4 and TNF_α even if in the present context the interest is particularly focused on the respiratory pathologies. In particular the compounds of the invention are useful for treating allergic and inflammatory diseases and above all for treating emphysema, chronic obstructive pulmonary disease (COPD) and chronic bronchitis specifically, asthma and allergic rhinithis.

The therapeutic doses shall be generally from 0.1 to 1,000 mg a day and from 1 to 100 mg by oral route for single administration.

A further object of the present invention are the pharmaceutical compositions containing a therapeutically effective amount of the compounds of formula I or pharmaceutically acceptable salts thereof in admixture with a suitable carrier.

The pharmaceutical compositions object of the invention can be liquid, suitable for the enteral or parenteral administration, and, preferably, solid such as tablets, capsules, granulates, suitable for the oral administration, or in a form suitable for the transdermal and inhalatory administration.

The preparation of the pharmaceutical compositions object of the invention can be carried out according to common techniques.

In order to better illustrate the invention the following examples are now given.

The ^{1}H-NMR spectra were run at 200 MHz, δ are in parts per million.

Example 1

5,6-Dimethoxy-3H-isobenzofuran-1-one

A suspension of 3,4-dimethoxy-benzoic acid (353.5 g, 1.94 moles) in HCHO (1.7 l, 24.5 moles) was prepared under mechanic stirring, cooled in ice, saturated with gaseous HCl (340 g, 9.32 moles), then gradually brought to 60°C. After one night the temperature was brought to the room values and further HCl (300 mg) was bubbled, then the temperature was brought again to 60°C for one night. The mixture was brought to small volume, taken up with water (1 l), neutralised with 28% NH_4OH (1.5 l) and kept at cool for 2 hours, then filtered. The filtrate was washed with water up to neutrality, then crystallised from CH_3OH (2 l) and dried under vacuum at 60°C to give 220 g of the title compound (yield: 58.65%).

^{1}H-NMR ($CDCl_3$): 7.28 and 6.28 (2s, 2H); 5.20 (s, 2H); 3.95 and 3.91 (2s, 6H).

Example 2

2-Formyl-4,5-dimethoxy-benzoic acid

A mixture of 5,6-dimethoxy-3H-isobenzofuran-1-one (10 g, 51.5 mmoles), obtained as described in example 1, under N_2 in CCl_4 (250 ml), N-bromo-succinimide (13.88 g, 77.25 mmoles) and benzoyl peroxide (320 mg, 1.23 mmoles) was kept under reflux for 2 hours, then cooled, filtered and washed with a 10% Na_2SO_3 solution (200 ml), then with water, anhydrified and brought to dryness. The residue was taken up with 5% HCl (100 ml) and kept under reflux for 4 hours, then the solution was cooled, basified with NaOH, washed with ethyl acetate and slowly re-acidified to give a precipitate which was filtered, washed with water, dried on P_2O_5 under vacuum to give 6.43 g of the title compound (yield: 60%).

Example 3

5,6-Dimethoxy-3-(triphenyl-λ^6-phosphanyl)-3H-isobenzofuran-1-one

A suspension of 2-formyl-4,5-dimethoxy-benzoic acid (6.43 g, 30.62 mmoles), obtained as described in example 2, triphenyl-phosphine (8.3 g, 30.62 mmoles), 30% HBr in acetic acid (8.26 ml, 30.62 mmoles) and glacial acetic acid (20 ml) under N_2 was heated at 90°C for 4.5 hours. The mixture was brought to dryness, re-dissolved in acetonitrile (50 ml) and diluted with ethyl ether up to turbidity, then cooled and filtered, and the filtrate was washed with ethyl ether and dried under vacuum to give 13.6 g of the title compound (yield: 83%).

^{1}H-NMR (DMSO): 8.35 and 7.31 (2s,2H); 8.03-7.66 (m,15H); 6.01 (s,1H); 3.84 and 3.45 (2s,6H).

Example 4

5,6-Dimethoxy-3-pyridin-4-ylmethylen-3H-isobenzofuran-1-one

Triethylamine (20 ml, 145 mmoles) was dropwise added to a suspension of 5,6-dimethoxy-3-(triphenyl-λ^6-phosphanyl)-3H-isobenzofuran-1-one (78 g, 145 mmoles), obtained as described in example 3, and 4-pyridincarboxaldehyde (13 ml, 145 mmoles) in CH_2Cl_2 (1 l), at room temperature under stirring. After 1.5 hours the mixture was filtered and evaporated and the residue was treated with ethanol under reflux, cooled and filtered. The mother liquors were chromatographed (eluent: 100% CH_2Cl_2, then with 1% CH_3OH) and the residue was brought to dryness and joined to the above filtrate to give 25 g of the title compound.

Example 5

6,7-Dimethoxy-4-pyridin-4-ylmethyl-2H-phthalazin-1-one

5,6-Dimethoxy-3-pyridin-4-ylmethylen-3H-isobenzofuran-1-one (25 g, 88.34 mmoles), obtained as described in example 4, was reacted with hydrazine hydrate (500 ml) for 2 hours at room temperature under stirring, then for 1 hour under reflux. The mixture was diluted with water (300 ml), cooled and filtered to give 23 g of the title compound (yield: 87%).

Example 6

1-Chloro-6,7-dimethoxy-4-pyridin-4-ylmethyl-phthalazine

A suspension of 6,7-dimethoxy-pyridin-4-ylmethyl-2H-phthalazin-1-one (10 g, 33.6 mmoles), obtained as described in example 5, in $POCl_3$ (70 ml) was heated at 90°C for 4

hours. $POCl_3$ was evaporated and the residue dissolved in water, a saturated $NaHCO_3$ solution and NaOH up to obtain a precipitate which was filtered and re-suspended in CH_3OH, brought to dryness, re-suspended in acetone and filtered again. The residue was dried at 45°C under vacuum to give 9.56 g of the title compound.

Example 7

8,9-Methoxy-6-pyridin-4-ylmethyl-tetrazol[5,1-a]phthalazine (Compound 1)

NaN_3 (103 mg, 1.583 mmoles) was added to a solution of 1-chloro-6,7-dimethoxy-4-pyridin-4-ylmethyl-phthalazine (500 mg, 1.583 mmoles), obtained as described in example 6, in DMF (4.5 ml) and the mixture was heated at 80°C for 16 hours. DMF was evaporated and the residue partitioned between water and CH_2Cl_2. The collected organic phases were anhydrified and brought to residue to give 420 mg of the title compound (yield: 82.3%).

^{1}H-NMR ($CDCl_3$): 8.55-8.52 (m, 2H); 8.00 (s, 1H); 7.25-7.22 (m, 3H); 4.59 (s, 2H); 4.10 and 3.90 (2s, 6H).

Example 8

6-Methoxy-3H-isobenzofuran-1-one

Formaldehyde 48% v/v (65 ml, 0.86 moles) under stirring, then 3-methoxy-benzoic acid (100 g, 0.66 moles) were added to concentrated HCl (1 l) and the mixture was heated at 100°C by checking the development of gas for 30 minutes. The cooling of the mixture brought to the formation of a precipitate which was filtered and put aside, while the mixture was washed with water, then with 5% NaOH. The new precipitate was extracted twice with CH_2Cl_2, the extract was anhydrified, concentrated, joined to the previously filtered solid, and both were dissolved in CH_2Cl_2 and treated with diethylamine (120 ml, 1.15 moles). After 24 hours it was extracted with 10% HCl and the phases were separated with CH_2Cl_2. The organic phase was washed with 10% NaOH, decoloured with charcoal, anhydrified and concentrated. The residue was dissolved in CH_2Cl_2 and treated, under stirring, with 10% HCl for 30 minutes. The organic phase was washed with water, anhydrified and concentrated. The residue was dissolved in CH_2Cl_2 and treated with 10% NaOH under stirring for 30 minutes. The organic phase was washed with water, dried and concentrated to give a solid which was crystallised from aqueous CH_3OH. The filtrate was dried at 50°C on P_2O_5, then

crystallised again from aqueous CH_3OH to give 35.28 g of the title compound (yield: 32%).

^{1}H-NMR ($CDCl_3$): 7.37-7.20 (m, 3H); 5.21 (s, 1H); 3.85 (s, 3H).

Example 9

3-Bromo-6-methoxy-3H-isobenzofuran-1-one

6-Methoxy-3H-isobenzofuran-1-one (35.28 g, 0.215 moles), obtained as described in example 8, suspended in CCl_4 (350 ml) under N_2, was added with N-bromo-succinimide (40 g, 0.225 moles), benzyl-peroxide in catalytic amount, then was slowly brought under reflux. After 2.5 hours the heating was stopped and the mixture was left standing overnight at room temperature. Further catalyst was added and it was heated for further 3.5 hours. The mixture was cooled in ice and filtered over celite by washing well with CCl_4, then concentrated to give 41 g of the title compound (yield: 78%).

^{1}H-NMR ($CDCl_3$): 7.50-7.25 (m, 4H); 3.87 (s, 3H).

Example 10

(5-Methoxy-3-oxo-1,3-dihydro-isobenzofuran-1-yl)triphenylphosphonium bromide

Triphenyphosphine (42 g, 0.16 moles) was added to 3-bromo-6-methoxy-3H-isobenzofuran-1-one (41 g, 0.169 moles), obtained as described in example 9, suspended in anhydrous acetonitrile (205 ml) under N_2. The mixture was heated under reflux and after 3 hours cooled and concentrated to give a solid which was treated with ethyl ether, filtered and concentrated under vacuum. There were thus obtained 74 g of the title compound (yield: 84%).

^{1}H-NMR ($CDCl_3$): 9.63 (s, 1H); 7.84-7.75 (m, 15H); 7.09-6.91 (m, 3H); 3.77 (s, 3H).

Example 11

3-(3,5-Dichloro-pyridin-4-ylmethylen)-6-methoxy-3H-isobenzofuran-1-one

Triethylamine (18.5 ml, 0.134 moles) was dropwise added to a suspension of (5-methoxy-3-oxo-1,3-dihydro-isobenzofuran-1-yl)triphenyl phosphonium bromide (74 g, 0.134 moles), obtained as described in example 10, and 3,5-dichloro-pyridin-4-carbaldehyde (23.6 g, 0.134 moles) in CH_2Cl_2 (500 ml) under N_2 by controlling the temperature with a water-bath. The mixture was kept under stirring overnight, then cooled and treated with 5% HCl. The phases were separated and the acid one was re-extracted with CH_2Cl_2, washed with water/NaCl, decoloured with charcoal, dried and concentrated under high vacuum. There were obtained

85.4 g of a crude which was used as such in the subsequent step. A sample of the crude was purified by flash chromatography (eluent: hexane/ethyl acetate 1:1).

^{1}H-NMR ($CDCl_3$): 8.60 (s, 2H); 7.77-6.68 (m, 4H); 3.80 (s,3H).

Example 12

4-(3,5-Dichloro-pyridin-4-ylmethyl)-7-methoxy-2H-phthalazin-1-one

Hydrazine (18.4 ml, 0.378 moles) was added to a suspension of 3-(3,5-dichloro-pyridin-4-ylmethylen)-6-methoxy-3H-isobenzofuran-1-one (24.4 g, 0.126 moles), obtained as described in example 11, in CH_3OH (200 ml), under N_2. The mixture was heated under reflux for 1 hour, then kept overnight at room temperature, cooled in ice, and the solid was filtered, washed with very cold CH_3OH and dried in oven at 50°C under vacuum, to give 33.3 g of the title compound (yield: 80%). m.p.: 259-262°C.

^{1}H-NMR ($CDCl_3$): 12.34 (s, 1H); 8.64 (s, 2H); 8.19-7.54 (m 3H); 4.58 (s, 2H); 3.95 (s, 3H).

Example 13

4-Chloro-1-(3,5-dichloro-pyridin-4-ylmethyl)-6-methoxy-phthalazine

$POCl_3$ (22.2 ml, 230 mmoles) was added to a suspension of 4-(3,5-dichloro-pyridin-4-ylmethyl)-7-methoxy-2H-phthalazin-1-one (10 g, 25.5 mmoles), obtained as described in example 12, in acetonitrile (300 ml) and the mixture was heated under reflux. After 3 hours the solution was concentrated, taken up with CH_2Cl_2, with water, and the pH was brought to 7-8 with Na_2CO_3. The organic phases were decoloured with charcoal, dried and concentrated to give 10 g of the title compound (stoichiometric yield).

^{1}H-NMR ($CDCl_3$): 8.50 (s, 2H); 8.13-7.54 (m, 3H); 4.88 (s, 2H); 4.04 (s, 3H).

Example 14

[4-(3,5-Dichloro-pyridin-4-ylmethyl)-7-methoxy-phthalazin-1-yl]-hydrazine

Hydrazine hydrate (0.81 ml, 0.84 g, 16.8 mmoles) was added to a solution under N_2 of 4-chloro-1-(3,5-dichloro-pyridin-4-ylmethyl)-6-methoxy-phthalazine (2 g, 5.6 mmoles), obtained as described in example 13, in ethanol (30 ml), and the mixture was kept under reflux for 24 hours, then cooled in ice and the resultant precipitate was filtered, washed with ethanol and ethyl ether and dried under vacuum at 50°C to give 2.14 g of the title compound (stoichiometric yield). m.p.: 297-299°C.

^{1}H-NMR (DMSO/D_2O): 8.61 (s, 2H); 7.95-7.20 (m, 3H); 4.48 (s, 2H); 3.87 (s, 3H).

Example 15

6-(3,5-Dichloro-pyridin-4-ylmethyl)-9-methoxy-3-methyl-[1,2,4]-triazole-[3,4-a]-phthalazine (Compound 2)

Acetic anhydride (0.2 ml, 0.22 g, 2.2 mmoles) was added to a suspension under N_2 of [4-(3,5-dichloro-pyridin-4-ylmethyl)-7-methoxy-phthalazin-1-yl]-hydrazine (0.7 g, 2 mmoles), obtained as described in example 14, in acetic acid, and the mixture was kept under reflux for 20 hours, then brought to small volume, taken up with CH_2Cl_2 and washed twice with 2.5% NaOH, then with water. The mixture was decoloured with charcoal, filtered over celite and concentrated under vacuum to give a solid which was triturated in ethyl ether to give 0.57 g of the title compound (yield: 77%). m.p.: 241.6-243.6°C.

^{1}H-NMR ($CDCl_3$): 8.55 (s, 2H); 8.06-7.34 (m, 3H); 4.76 (s, 2H); 4.03 (s, 3H); 2.46 (s, 3H).

Example 16

6-(3,5-Dichloro-pyridin-4-ylmethyl)-9-methoxy-tetrazolo[5,1-a]-phthalazine (Compound 3)

NaN_3 was added to a solution under N_2 of 4-chloro-1-(3,5-dichloro-pyridin-4-ylmethyl)-6-methoxy-phthalazine (1 g, 2.82 mmoles), obtained as described in example 13, in anhydrous DMF (20 ml) and the mixture was heated at 80°C overnight, then at 120°C for 7 hours, then poured into water (10 volumes) and extracted 3 times with CH_2Cl_2, dried and concentrated under vacuum to give a solid which was purified by flash chromatography (eluent: 60:80 petrolatum/ethyl acetate 6:4). The eluate was crystallised from acetonitrile (75 ml) to give 0.36 g of the title compound (yield: 78.5%). m. p.: 275-276°C.

^{1}H-NMR ($CDCl_3$): 8.57 (s, 2H); 8.22 (d, 1H, JHH=8.7Hz); 8.246 (d, 1H, JHH=2.5Hz); 7.57 (dd, 1H); 4.89 (s, 2H); 4.10 (s, 3H).

Example 17

5-(3,5-Dichloro-pyridin-4-ylmethyl)-8-methoxy-1,3,3a,4-tetraaza-cyclopentan[a]naphthalene (Compound 4)

NaH (0.14 g, 3.38 mmoles) was added to a solution under N_2 of 1H-tetrazole (0.315g, 4.5 mmoles) in anhydrous DMF (10 ml) and the mixture was kept under stirring for 2 hours. 4-Chloro-1-(3,5-dichloro-pyridin-4-ylmethyl)-6-methoxy-phthalazine (0.8 g, 2.25 mmoles),

obtained as described in example 13, was added and it was heated at 80°C. then at 100°C overnight. The mixture was poured into water and extracted with CH_2Cl_2. The organic phase containing an insoluble was concentrated under vacuum and taken up with CH_3OH. A solid was obtained which, triturated with hot CH_3OH then cooled, was removed by filtration. The mother liquors were brought to dryness to give a solid which was flash chromatographed (eluent: CH_2Cl_2/CH_3OH 98:2), to yield a solid which, triturated with ethyl ether, gave 0.18 g of the title compound (yield: 22%). m.p.: 231.3-232.3°C (dec.).

^{1}H-NMR ($CDCl_3$): 8.77 (s, 1H); 8.56 (s, 2H); 8.09-8.03 (m, 2H); 7.40 (dd, 1H, JHH=9Hz, J2HH=2.7Hz); 4.76 (s, 2H); 4.04 (s, 3H).

Example 18

Evaluation of the PDE 4 enzyme inhibition

a) Purification of human polymorphonucleate leukocytes

The polymorphonucleate leukocytes (PMNs) were isolated from peripheral blood of healthy volunteers according to what described by Boyum A., Scand. J. Immunol., 1976, 5th suppl., 9). Shortly, the isolation of the PMNs was effected by Ficoll-Paque gradient centrifugation followed by sedimentation on dextrane and the erythrocyte contamination was eliminated by hypotonic lysis.

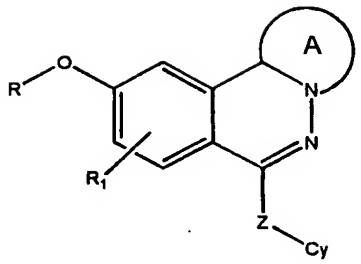
b) PDE 4 enzyme purification

The human PMNs were re-suspended in TRIS/HCl buffer (10mM pH 7.8) containing $MgCl_2$ (5mM), EGTA (4mM), mercaptoethanol (5mM), TRITON-X100 (1%), pepstatin A (1μM), PMSF (100μM) and leupeptin (1μM), and homogenised by Polytron. The homogenate was centrifuged at 25,000 x g for 30 minutes at 4°C and the supernatant was used for the PDE 4 enzyme purification by ion exchange chromatography using the FPLC technique according to what described by Schudt C. et al., Naunyn-Schmidberg's Arch. Pharmacol., 1991, *334*, 682. The supernatant was seeded on an UNO Q12 column (Bio-Rad) and the enzyme was eluted by sodium acetate gradient from 50mM to 1M. The fractions containing enzymatic activity were collected, dialysed against water and concentrated. The resulting PDE 4 enzyme was stored at -20°C in the presence of ethylenglycole (30%, v/v) until the use.

c) PDE 4 enzyme inhibition

The enzyme activity was evaluated with an Amersham kit based on the SPA (Scintillation Proximity Assay) technique. The enzymatic reaction was effected in a total volume of 100 µl of TRIS/HCl buffer (50mM, pH7.5), $MgCl_2$ (8.3mM), EGTA (1.7mM), cAMP (1µM) and [^{3}H]cAMP (~100.000 dpm) as tracer. The compounds of the invention were added at the selected concentrations. The reaction was started by adding the enzyme (15 µg protein/ml), went on for 40 minutes at 30°C and stopped by adding 50 µl of suspension of SPA particles. The radioactivity due to the particles was measured in a β-emitting counter. The results are expressed as percent activity versus the control present in each experiment. The IC_{50} values were calculated over 9 equidistant concentrations in logarithmic scale using a 4-parameters logistic function by software. The compounds of the present invention showed to selectively inhibit PDE 4: for example, Compound 2 gave a value of IC_{50}=207nM.

1) Compounds of formula



(I)

wherein

A is a 5-7 membered heterocycle containing from 1 to 4 nitrogen atoms, optionally partially or totally unsaturated, and optionally substituted by a (C_{1-4})alkyl group in turn optionally substituted;

Z is NH, methylene, a C_{2-6} alkylene chain optionally branched and/or unsaturated and/or interrupted by a C_{5-7} cycloalkyl residue;

Cy is phenyl or heterocycle optionally substituted by one or more substituents, or a COR_4 group wherein R_4 is hydroxy, alkoxy, amino optionally substituted by one or two (C_{1-6})alkyl groups or by hydroxy;

R is a (C_{1-6})alkyl or polyfluoro(C_{1-6})alkyl group;

R_1 is hydrogen; a (C_{1-8})-alkyl, (C_{2-8})-alkenyl or (C_{2-8})-alkynyl group optionally substituted by hydroxy, oxo, aryl or heterocycle, and optionally interrupted by one or more heteroatoms or heterogroups; a (C_{1-4})alkoxy group or a (C_{4-7})cycloalkoxy group optionally containing an oxygen atom and optionally substituted by a polar substituent in the cyclic moiety, aryloxy, aryl-(C_{1-10})-alkoxy;

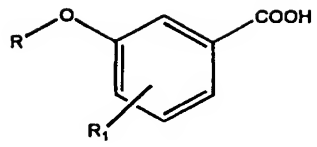
the N→O derivatives of the compounds of formula I and the pharmaceutically acceptable salts thereof.

2) Compounds according to claim 1 wherein Z is methylene or a C_{2-6} alkylene chain.

3) Compounds according to claim 1 wherein Z is methylene or a C_{2-6} alkylene chain; and Cy is a heterocycle optionally substituted by one or more substituents.

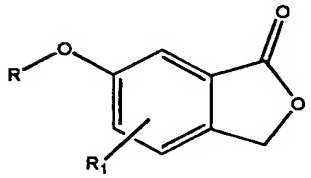
4) Compounds according to claim 1 wherein Z is methylene; and Cy is pyridine substituted by two substituents.

5) Process for the preparation of a compound according to claim 1 wherein Z is different from NH, characterised in that an acid of formula



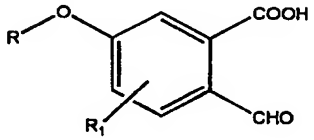
(II)

wherein R and R_1 are as defined in claim 1, by reaction with formaldehyde/HCl gives a compound of formula



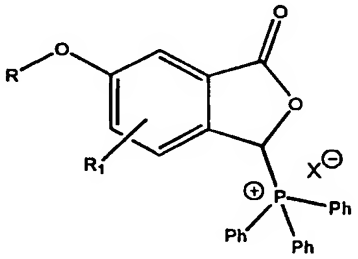
(III)

wherein R and R_1 are as above defined, which is oxidised and hydrolysed to give a compound of formula



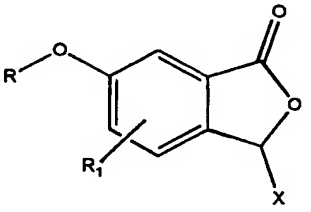
(IV)

wherein R and R_1 are as above defined, which is treated with a hydrohalogenidric acid and triphenylphosphine to give a compound of formula



(V)

wherein R and R_1 are as above defined, this compound being also obtainable from compound III by radicalic halogenation to give the compound of formula

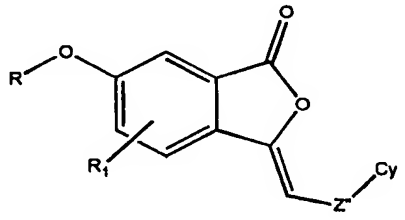


(IIIa)

wherein R and R_1 are as above defined, and X is chlorine or bromine, which gives compound V by treatment with triphenylphosphine; said compound of formula V treated with an aldheyde of formula

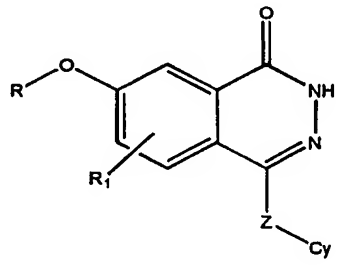
Cy-Z"-CHO (VI)

wherein Cy is as defined in claim 1 and Z" is a C_{1-5} alkylene chain optionally branched and/or unsaturated and/or interrupted by a C_{5-7} cycloalkyl residue, or it is absent, in the presence of an organic base gives a compound of formula



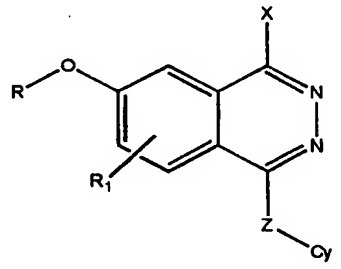
(VII)

wherein R, R_1, Z" and Cy are as above defined, which is treated with hydrazine to give a compound of formula



(VIII)

wherein R, R_1 and Cy are as above defined and Z has the meanings reported in claim 1 but amino, which is treated with a halogenating agent to give a compound of formula



(IX)

wherein R, R_1 and Cy are as above defined, and X is chlorine or bromine, which is treated with a suitable nucleophile or with hydrazine and then with a suitable acylating agent.

6. A pharmaceutical composition containing a therapeutically effective amount of a compound according to claim 1 in admixture with a suitable carrier.

7. A pharmaceutical composition according to claim 6 for the treatment of allergic and inflammatory pathologies.

8. A pharmaceutical composition according to claim 6 for the treatment of respiratory diseases.

INTERNATIONAL SEARCH REPORT

Inter .onal Application No
PCT/EP 99/07304

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/5025 //(C07D487/04,237:00;257:00), (C07D487/04,237:00,249:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 32456 A (ALVAREZ BUILLA JULIO G ;GARCIA NAVIO JOSE LUIS (ES); SIRO HERRERO) 1 July 1999 (1999-07-01) the whole document ---	1-8
Y	WO 98 21208 A (BYK GULDEN LOMBERG CHEM FAB ;FLOCKERZI DIETER (DE)) 22 May 1998 (1998-05-22) cited in the application the whole document ---	1-8
Y	WO 93 07146 A (SYNTEX INC) 15 April 1993 (1993-04-15) the whole document ---	1-8
Y	EP 0 722 936 A (EISAI CO LTD) 24 July 1996 (1996-07-24) the whole document ---	1-8
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 2000	16/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stellmach, J

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr ...nal Application No
PCT/EP 99/07304

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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